Application No.: 09/953,344 Docket No.: 22220-00003-US

REMARKS

Claims 1-12 are pending in the application. Claims 1-9 are under consideration as the group elected in response to Restriction in the application. Claim 1-9 stand rejected.

ITEM 1. Applicant reserves the right to pursue restricted species in continuation applications.

ITEM 2. Examiner's statement to the effect that "examination will be confined to examination of the elected invention" is acknowledged but this acknowledgement does not constitute an admission by Applicant that claims 2 and 4 are not species. Indeed, the specification provides ample evidence of invention of various species in addition to influenza.

Specification

ITEM 3. Examiner identified an incorrect reference to a Table. The specification is corrected to recite Table 3 on page 54, line 16.

Rejections of Claims Under 35 USC § 112

ITEM 5. Claims 3 and 4 are rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter. In particular the Applicant has allegedly failed to describe the structural characteristics of reduced antigen.

The process of reducing can comprise "rendering, cooking, drying, dehydrating, digesting, evaporating, pulverizing, sonicating, protein concentrating, breaking into small pieces, reducing to powder or granules, blasting, enzyme digestion, dialysis, ultrafiltration, separating by gel migration, and ion exchange chromatography" (page 29, lines 9-13). These processes are standard reducing processes in the art.

This statement is exemplified in the context of influenza virus on page 62, paragraph 4, which states: "The whole mass of egg liquid is obtained by breaking the shells of eggs

[previously inoculated with influenza virus] and is simply spray-dried at a blowing temperature of 175°C. This reduction step results in dry egg powder comprised substantially of spherical particles having an average particle diameter of 100 micrometer." In consequence, in one embodiment, the reduced antigen of the invention can be particles that are 100 micrometer in average diameter.

Thus the structural characteristics of the reduced influenza antigen are identified with particularity.

The specification also provides process disclosure and structural characteristics for other "reduced" antigens. For example the process of reducing vaccine pathogen from a source such as blood or plasma down to powder or granules is explicit (page 35, 1st full paragraph): "The blood is next dried to form a beige/brown powdery substance. When this powder is washed and dried again it results in white crystalline powder. The resulting powdery substance can have a particle size of about 0.5 to about 30 microns or higher. Optionally, the powder can be further compacted or compressed (around 1200 to 1400 psi) to form granules and screened or otherwise separated by size to increase homogeneity. The resulting granulated particle size is at least about 50 microns. Preferably the size is greater than about 100 microns in diameter."

Reconsideration of the rejection is respectfully requested.

ITEM 6. Claim 7 is rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter. Specifically, a comma was omitted between terms fungi and influenza.

Claim 7 has been amended in accordance with the suggestion of Examiner to correct a typographical error. No new matter has been added with this change.

ITEM 8. Claims 3-9 were rejected under 35 USC 112, first paragraph, as not enabling those skilled in the art to make viral vaccines other than inactivated influenza vaccine. Examiner

also states that said claims read broadly on any pathogen including live inactivated pathogen. Reconsideration is requested.

Claim 3 calls for "reduced viral pathogen formulated as an oral pill". The definition for the process of reduction is provided on page 29 of the specification. See also the discussion, above. It is understood from the specification that the process of reduction does not result in live pathogen. Moreover, none of the specific Examples of making various vaccines disclose a process of making or using live or attenuated pathogen. Furthermore Examiner himself states in item 5 of the Office Action (supra) that "[F]or the purposes of this action, it is being assumed that the term reduced includes process of heating or other means of inactivating the pathogen."

In consequence, the rejection of claim 3 for lack of enablement should be withdrawn. Claim 4, which depends from claim 3, incorporates all the limitations thereof. The rejection of claim 4 should be withdrawn for the reasons presented for claim 3.

Claim 5 is directed to an immunogen. The term "immunogen" as used in the application does not encompass live pathogen. In consequence, when construed in light of the disclosure, claim 5 and the claims that depend therefrom do not read on live pathogen. Withdrawal of the rejection is requested.

Rejections of claims under 35 USC § 102

ITEM 10. Claims 1 and 2 are rejected over Avtushenko et al (J Biotechnol 1996;44:21-28) as anticipated under 102(b). Reconsideration of the rejection is requested for the following reasons.

A rejection for anticipation under section 102(b) requires that each and every limitation of the claimed invention be present in the cited art. MPEP 2131. See also In re Bond, 910 F.2d 831, 832, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). The cited reference is missing a claim limitation or element since Avtushenko et al., does not teach the 'heat-inactivated' viral antigen(s) of the invention. Rather, Avtushenko et al. teaches 'emulsion-inactivated' vaccine (page 21, Abstract; page 22, Materials and Methods). Nowhere can the 'heat-inactivated'

vaccine of claims 1 and 2 be found in the cited reference. Claim 2 incorporates all the elements of claim 1 from which it depends. Withdrawal of the rejection is respectfully requested.

ITEM 11. Claims 3-5 and 7-8 are rejected as anticipated by Barrett et al. (WO 00/47222 and corresponding US Patent No. 6,635,246).

Claim 3 calls for 'reduced viral pathogen formulated as an oral pill' as means of inducing immunity. The process of "reducing" as used in the instant invention was discussed above. Barrett et al. disclose 'inactivated' influenza virus. Scrutiny of the Barrett et al. disclosure reveals that influenza virus is inactivated either by emulsion-inactivation as per Avtushenko et al. (Column 1, line 45) or by treatment with 0.025% formalin (Column 4, line 25). Nowhere does Barrett et al. disclose the reduced viral pathogen of the present invention. The present disclosure also defines that the process of reduction is distinct from other steps in vaccine preparation such as denaturation, which is defined as "heating, treating with a detergent, oxidizing, aldehyde treatment, subjecting to extreme pH conditions like acid or alkaline treatment, the preferred means are however the thermal denaturation". Clearly, the inactivated influenza virus of Barrett et al. falls under the category of denatured pathogen since emulsion and formalin are detergent and aldehyde, respectively. Thus, Barrett et al. does not disclose all the elements of the claimed invention, nor does it render the claim obvious. The rejection of claim 3 and dependent claim 4 is respectfully requested to be withdrawn.

Barrett et al. explicitly teach that the invention comprises "at least one inactivated influenza virus antigen and aluminum as an adjuvant for nasal or oral application' (US Patent column 2, ll. 38-42 and throughout the specification). The reason Barrett et al. includes an adjuvant as a prerequisite for nasal or oral vaccine is that the vaccines of the prior art, which lacked an adjuvant, had failed to induce immunity (Col. 1, ll. 54-60). Thus, the oral vaccine of Barrett et al. is specifically the combination of immunogen plus adjuvant. Only this combination is taught as capable of inducing the desired immune response. In Barrett et al., the immunogen without adjuvant fails to elicit an immune response.

By contrast, claim 5 is explicit that it is the immunogen that 'retains the ability to elicit immune response'. The term 'immunogen' as found in said claim is defined in the present specification as being "a single bacterial/viral protein or fragment thereof." (Page 2, l. 30).

Withdrawal of the rejection of claim 5, and claims 7 and 8 which depends therefrom, is respectfully requested.

ITEM 12. Claims 5-8 are rejected by the Examiner under 102(b) as allegedly anticipated by Waldman et al., (Am J Med Sci 1986;192:367-71). Reconsideration is requested.

Waldman et al. are considered to have been trail-blazers in the oral vaccinology field. They describe in their paper an experiment whereby human volunteers received 'subunit' influenza vaccine available commercially from Parke-Davis either by injection or as an oral enteric-coated capsule. In volunteers, the oral vaccine failed to elicit serum antibodies but did elicit secretory antibody production, a sign of immune response. See Tables 3 & 4 of Waldman et al. However, as indicated in the last paragraph in the left column of their publication (page 370), the volunteers who were subjected to oral vaccine were already immunized, i.e., had already antibodies against influenza.

By contrast, claim 5 requires that the immunogen can elicit an immune response in a host in need of immune response. Clearly, the volunteers of Waldman et al. are not in need of immune response since they already had an immune response. Waldman et al. did not teach administration of vaccine to a naive population in need of immune response (last paragraph, left column, page 370). The article fails to teach what will be the immune response in those who actually need it. Moreover, the authors of Waldman et al. are at loss as to what will be the immune response in such a population, when and if, they are given the oral vaccine. They admit that this has "never been reported in humans". Moreover, in other host species the administration of oral vaccine produced an effect opposite to the desired immune response (page 370, the last sentence of the article). Thus, Waldman et al. does not anticipate claim 5, nor render it obvious. Claims 6 to 8 depend from claim 5 and are not anticipated by Waldman et al. for the same reasons.

The rejection is respectfully requested to be withdrawn.

Rejections of claims under 35 USC § 103

ITEM 14. Claims 1-9 are rejected as being unpatentable over either Zakay-Rones et al. (WO97/14434) or Dutcher et al., (US Patent No. 3,060,094), either of these references in view of Smith et al., (US Patent 6,245,532), or Avtushenko et al., (J Biotechnol 1996;44:21-28) and further in view of Sokoll et al., (US Patent 6,623,764).

According to the Examiner, Zakay-Rones and Dutcher teach making and using a vaccine comprising heat-inactivated influenza virus and Smith teaches non-inactivated influenza A and B combination vaccine. Examiner also states that it would have been obvious to those skilled in the art to reasonably expect success when such vaccines are used. However, Examiner admits that these references taken together with Avtushenko et al., fail to teach an oral vaccine as a simple pill. Thus, in order to make obvious the vaccine of the present invention, one would have to combine these teachings with the Sokoll reference. Sokoll et al. disclose a biodegradable polyester carrier particle for delivery of an immunogenic composition of agents like viral immunogens. Sokoll further teaches that these carriers can be formulated as an oral tablet but he fails to teach heat-inactivated influenza viruses. According to the Examiner it would have been within reach of practitioner in the art to determine specific dosages (percent) of antigen to use in the pill. For these reasons the present invention is allegedly obvious to those skilled in the art.

In brief, Examiner recognizes that a combination of four references (Zakay-Rones; Dutcher; Smith; and Avtushenko) do not render obvious the invention as claimed. Examiner then asserts that a fifth reference, Sokoll et al., is needed to teach the instant invention.

As an initial matter, Examiner's assertion suffers from hindsight. The Smith patent and the Sokoll patent are non-analogous in that they do not share any U.S. classification groups. See MPEP 707.07(f). Smith is directed to recombinant hemagglutinin as a vaccine. Sokoll is directed to polyester microparticles. Thus one of skill in the art of vaccine development could not reasonably have been expected to be sufficiently knowledgeable about polyester microparticles to combine the Sokoll and Smith patents. Conversely, one of skill in the field of

polyester microparticles could not reasonably have been expected to be knowledgeable about recombinant hemagglutinin as a potential vaccine. Despite Examiner's assertions, there can be no motivation to combine five references as disparate as the cited references. For at least this reason, the rejection should be withdrawn.

Rejection of a claim by reliance on a large number of references "without more" has been upheld. *In re Gorman* 993 F.2d. 982, 18 USPQ 2d 1885 (Fed. Cir. 1991). In *Gorman* a candy confection having the shape of a thumb was rejected over a combination of several references. Candy making has been highly developed for centuries. Unlike candy making, vaccine development is conceptually complex and the field is not as minutely differentiated. Thus, in the instant rejection, the "without more" that the court required in *Gorman* is met by the nature of the subject matter field. Moreover, a combination of references that "skirt around" the claimed invention does not show obviousness. *Hybridtech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 USPQ 51, 93 (Fed. Cir. 1986). For these additional reasons the rejection should be withdrawn.

Furthermore, Applicant respectfully asserts that Examiner has construed the disclosure of Sokoll et al. beyond the reasonable limits of the specification, as follows.

Examiner asserts that, in the Abstract, Sokoll et al. teaches "biodegradable carrier particles for the delivery of immunogenic compositions." Office Action, page 7, l. 6. The Abstract actually recites that Sokoll et al is directed to "[c]opolymers designed for use as particulate carriers containing functionalizable amino acid subunits for coupling with targeting ligands." Abstract.

Sokoll et al does not teach an immunogen not associated with polyester copolymers. Moreover, Sokoll et al. does not teach that administration of an immunogen in the absence of polyester copolymers is effective in producing an immune response. In contrast to Sokoll, claims 1-9 of the instant invention do not require copolymers containing functionalizable amino acid subunits.

Examiner further asserts that Sokoll et al further indicates that these carriers may be formulated to deliver antigens or antigens with an adjuvant through oral administration routes. Rather, Sokoll et al. recites that "[t]he present invention is directed toward the production of a novel and useful [polyester] polymer that has properties suitable for manufacturing by various processes into microparticles and microspheres." Col. 3, l. 66 to col. 4, l. 2.

By contrast, claims 1 and 2 of the instant invention are directed to a vaccine comprising heat-inactivated viral antigen. Also, claims 3 and 4 are directed to a composition comprising a reduced viral pathogen. Claim 5, and claims that depend therefrom, are directed to an immunogen that retains the ability to elicit an immune response in a host in need of immune response.

Examiner also points to Sokoll et al. as disclosing that the [polyester-containing] compositions of Sokoll et al. can be formed as solutions, suspensions, tablets, pills etc.

Again, Sokoll et al. is directed to use of polyester copolymers having amino acid moieties capable of coupling with immunogens.

For at least these reasons, Sokoll et al. cannot compensate for the deficiencies of the disclosures of the Zakay-Rones; Dutcher; Smith; or Avtushenko references. Thus, the combination of references does not render obvious claims 1, 3 or 5, or claims dependent therefrom. Withdrawal of the rejection is requested.

ITEM 15. Claims 5-9 are rejected over Sokoll reference (supra) as rendering obvious the inclusion of influenza virus and an antigen in a pill for oral administration.

The Sokoll reference teaches a process of making polyester co-polymers which can be then made as biodegradable microparticles. The microparticles, when mixed with various substances like drugs or vaccine antigens can form microspheres to serve as means of delivery of the substances. In the paragraph starting from line 4 in column 14, Sokoll teaches that an immunogenic composition made by the claimed process may take the form of tablets and pills, among other forms. However that same paragraph explicitly teaches that Sokoll's formulation,

when given orally, has to be co-administered with another preparation such as sodium bicarbonate to neutralize stomach acidity. According to Sokoll, the neutralizing agent is necessary to protect the biological activity of the vaccine against digestive degradation.

Clearly, Sokoll's hypothetical oral vaccine pill is deficient in overcoming the cornerstone problem that has prevented generations of vaccinologists from creating a vaccine available as a simple oral pill. The Applicant advises that Sokoll's hypothetical pill will not retain the ability to elicit an immune response if given as an oral but 'biodegradable' pill.

Thus, for at least these reasons the obviousness rejection over Sokoll et al should be withdrawn.

ITEM 16. Claim 9 is rejected under USC 103 (a) as being unpatentable over Barrett, Avtushenko, or Waldman as applied supra.

Claim 9 depends from claim 5. Claim 5 was not rejected over Avtushenko. Claim 5 is not anticipated or rendered obvious by Bennett for the reasons presented above, nor is it anticipated or rendered obvious by Waldman, for the reasons presented. Thus, if the independent claim is not anticipated and is nonobvious, then any claim depending therefrom is nonobvious. MPEP 2143.03.

Examiner does not use Lelie et al., Eisenthal et al., or Moloveanu et al. as basis for rejection but states that they are pertinent or redundant. Lelie et al. does not teach preparation or use of an oral vaccine. Eisenthal et al. does not disclose preparation of a vaccine, let alone an oral vaccine. Moloveanu et al. does not disclose preparation of a heat-inactivated oral vaccine. Thus, none of these references anticipate or render obvious the instant invention as claimed.

For at least the reasons given, reconsideration of all rejections and objections is respectfully requested. Applicant requests timely allowance of all pending claims.

A power of attorney naming the undersigned is submitted with this Reply. If Examiner believes for any reason that communication by telephone would facilitate prosecution of the application, the Examiner is encouraged to call at the number listed below.

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Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 22-0185, under Order No. 22220-00003-US from which the undersigned is authorized to draw.

Dated: March 16, 2004

Respectfully submitted,

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